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BAP Position Statement:

Off-label prescribing of psychotropic medication to children and adolescents

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Paper

The 'off-label' use of medicines for children and adolescents remains a common and important issue for prescribing practice across child and adolescent psychiatry, paediatrics and primary care (Arango 2015; Persico et al. 2015). The issues regarding off-label use of drugs in neonates, infants, children younger than 2 years and children with chronic and/or rare diseases are particularly complex and lie outside the scope of this position statement. Here we will focus only on psychotropic drug treatment which plays an essential part in the comprehensive management of a range of child and adolescent psychiatric disorders (Taylor 2015).

Despite a growing evidence-base for drug treatment in child and adolescent psychiatric disorders, much psychotropic medication continues to be prescribed 'off-label' i.e. outside the limits of the marketing authorisation or product license. For example, the 'off-label' prescribing of antipsychotics for children age 7–12 years of age in primary care within the UK almost tripled between 1992 and 2005 with the prescribing of second generation antipsychotic increasing 60-fold from 1994 to 2005 (Rani et al. 2008). It remains unclear whether this increase in 'off-label' prescribing of antipsychotics to children should be raising concerns about safety, or be viewed as an indication of appropriate clinical practice in the management of often complex and debilitating conditions. The truth is likely to be a combination of the two.

The reasons for and implications of 'off-label' prescribing, including the potential clinical benefits/risks and medico-legal implications, are often poorly understood by both patients and prescribers. An important unintended consequence of the uncertainties and confusion surrounding the status of 'off-label' prescribing for children and young people may be that effective drug treatments are being withheld or underused. This BAP Position Statement aims to clarify these issues, challenge some of the myths surrounding 'off-label' prescribing for children and young and offer practical guidance for prescribers.

What does 'off label' prescribing mean?

In the UK, licensed medicines are those that have received a marketing authorisation (previously referred to as product license) as determined by the Human Medicines Regulations 2012 (Medicines Regulatory Group 2012). This license allows a producer to market (sell, advertise) a medicine for a specific indication in a specific group of patients. 'Off-label' prescribing occurs when medication use falls outside the scope of the marketing authorisation with respect to one, or more, of 4 key domains (the '4 D's'): i) the Disorder being treated, ii) the Demographics (primarily age) of the patient, iii) the Dosage being prescribed and route of administration and iii) the Duration of treatment (Baldwin and Kosky 2007). Prescribing a medicine in a circumstance that is specified as 'contraindicated' would also constitute 'off-label' use. It is, however, important to recognise that prescribing drugs that are contraindicated is not identical to using a drug outside the '4 D's' as the latter use may often (as discussed later) be very appropriate. An example of such a contraindication is the prescribing of methylphenidate to a child with ADHD who also has a structural cardiac anomaly (Joint Formulary Committee).

Where medication use falls outside the scope of the marketing authorisation '4 D's', or it is contraindicated, this can be termed as 'use of licensed drugs for an unlicensed indication', also referred to as 'off-label' or 'off-license' prescribing. The terms 'off-label' or 'off-license' prescribing of licensed drugs should be distinguished from 'unlicensed' prescribing which refers to prescribing of a drug or formulation of drugs that has not yet received marketing authorisation for any indication or prescribing a drug when marketing authorisation has been withdrawn.

Why are psychotropic medications often prescribed 'off-label' for children and adolescents?

Marketing authorisation (the product license) is required in order for a manufacturer to sell, advertise and promote a drug for the defined condition and population. Potential new medicines developed by pharmaceutical companies are typically tested first for safety and efficacy in the population most likely to represent the major areas of use and most commonly this will be in adults. Very few psychotropic medications are developed for and tested first in a paediatric population, an example

being ADHD medications where adult testing and marketing authorisation came later. Until relatively recently there were no statutory requirements for drugs to be tested in younger age groups and although companies were encouraged to undertake studies in children and adolescents, few did. This meant that for most drugs data relating to safety and effectiveness in young people are extremely limited, not only at the point of entry into the market but continuing throughout the life of the drug.

This situation has changed considerably for new medications in recent years. In the USA, the US Food and Drug Administration (FDA) enacted a series of legislations in the late 1990s and early 2000s that both required pharmaceutical companies to gather efficacy and safety data on any new medications being developed that may at some stage in their life be used in the paediatric population (0-17 years) and incentivised them for doing so. In 2012, these initiatives were enshrined in the US FDA's Safety and Innovations Act (US Food and Drug Administration 2012). In Europe, the European Medicines Agency (EMA) acting on behalf of the European Commission (EC) identified that more than 50% of all medicines used for children had not been tested for use in this specific age group and that the availability of child-appropriate medicines was generally unsatisfactory.

Following the initiative taken by the US FDA, the EC developed the Paediatric Regulation (European Medicines Agency 2007) (EMA), which established a system of obligations, rewards and incentives, to ensure that medicines are regularly researched, developed and authorised to meet the therapeutic needs of children. This regulation compels companies to consider the potential paediatric use of medicinal products they develop and conduct a specific programme of research where there is potential for use in this population.

The objectives of both US and EU legislation is to improve the availability of information on the use of medicines for children, to facilitate the development and availability of medicines and to ensure that those medicines for use in children are of high quality, safe, ethically researched and authorised appropriately. At the same time it ensures that children are not subjected to unnecessary trials or

that the authorisation of medicines for use in adults is not delayed whilst waiting for this evidence. The major consequences of the EU Paediatric Regulation are described in Box 1.

Whilst this US and EU legislation is mainly targeted at new medications the EMA also offered incentives to marketing authorisation holders if they developed and implemented a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), for off-patent medications. To get a PUMA it is necessary to conduct a series of studies that have been agreed with the EMA and described in a Paediatric Investigation Plan (PIP). If successful, these result in the award of the PUMA and gives an extension of existing marketing authorisation to the paediatric population and a period of exclusivity to the company. The process of obtaining a modification to a product license, whether through a PUMA or otherwise, is complex and very costly, so even with the incentives now being offered many companies remain reluctant to conduct these studies, even when there is good placebo-controlled evidence of efficacy and safety in this group. This is even more evident for non-commercial academic consortia trying to obtain a PUMA for an off-patent drug. Whilst the EU FP7 research programme sponsored some research programmes aimed at developing PIPs including one for the use of risperidone in conduct disorder; Paediatric European Risperidone Studies (PERS), the monies available through these grants was limited and few if any have been successful in obtaining a PUMA.

Licensing of medicines is relatively standardised across the EU although there are still differences between individual member states with respect individual drugs. Outwith the EU these arrangements are less consistent and vary considerably across other jurisdictions. Examples of drugs licensed prior to the introduction of the new legislations and for which there is a relatively good evidence base in paediatric populations but which lack marketing authorisation and are therefore prescribed 'off-label' in children and adolescents in Europe include; sertraline for treatment of anxiety disorders and Obsessive Compulsive Disorder (OCD), risperidone for the treatment of psychosis and schizophrenia, and clonidine for the treatment of tics/Tourette syndrome.

For other drugs, licensed prior to the legal changes, while safety and efficacy data from trials exists for adults for a specific condition, sufficient trial evidence is not available for children and adolescents with the same disorder. As clinical trials are expensive and time consuming, companies have often chosen not to run trials with children and young people as there may be no anticipated commercial gain through this relatively small market. For example, there remains a paucity of marketing authorisations for psychotropics to treat Bipolar Disorder in children and adolescents despite the considerable unmet need of those affected by this infrequently diagnosed disorder particularly in the UK (Sharma et al. 2011).

For some conditions such as OCD and Bipolar Disorder evidence suggests it is reasonable to extrapolate safety and efficacy data from adults to adolescents, while in other conditions such as depression there appear to be important age-related differences in medication response. The British Association for Psychopharmacology (BAP) suggested that it would be reasonable to extrapolate knowledge about treatment response in adults to children and adolescents for schizophrenia (psychosis) or OCD, but that caution is required in the case of patients with anxiety disorders (Baldwin et al. 2014) and mood disorders (Cleare et al. 2015). There is also emerging evidence that adolescents may be more sensitive to the metabolic adverse effects of atypical antipsychotics, in particular olanzapine, which highlights the limitations of extrapolating safety and data from adults to children and young people (Kryzhanovskaya et al. 2012).

What are the implications of prescribing 'off-label' for children and adolescents?

1. Safety and efficacy

Prescribing within the marketing authorisation or product license does not guarantee safety or effectiveness. For example, in the management of Tourette syndrome in children, the use of Haloperidol, licensed for use up to 10 mg/day, may carry significantly greater risks of harm than the 'off-label' use of clonidine. Dexamfetamine (immediate release) is licensed in the UK for treatment of ADHD in children from age 3. However, NICE CG 72 Guidance for ADHD (NICE 2008) based on systematic review of evidence and expert clinical consensus recommends that stimulant medications should not be routinely used in pre-school children under age 5.

Given the limitations of the product license, the responsibility of the prescriber is to understand and appraise the evidence-base for all medications they use regardless of whether or not they have marketing authorisation. It was never intended to be a requirement that clinicians must only prescribe a medication within the limits of its marketing authorisation. Nor should it be a requirement that drugs with marketing authorisation for use in children should always be prescribed in preference to 'off-label' medications, as this may lead to the withholding of more effective and safer 'off-label' alternatives.

2. Medico-legal considerations in the UK

There may be reluctance on the part of child and adolescent psychiatrists or paediatricians to recommend the use 'off-label' psychotropics and from General Practitioners (GPs) to prescribe drugs 'off-label' even under the auspices of a shared care protocol. This reluctance is often a result of a misplaced medico-legal fear of litigation should a practitioner prescribe a medication 'off-label' and the patient develops an adverse reaction. It is important to make it clear that independent prescribers can prescribe any medication (licensed, unlicensed or 'off-label') so long as this prescription would be supported by a reasonable body of medical opinion (UK Medical Act 1983). Limitations of the marketing authorisation should not preclude unlicensed use where clinically appropriate.

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines, and also inform the patient and/or their carer that the prescribed medicine is either unlicensed or being used 'off label'. In circumstances where 'off-label' prescribing for children and adolescents is supported by an evidence base and ideally, published clinical guidelines, then 'off-label' prescribing practice would be easily defensible. However, in circumstances where the evidence-base is less clear cut but there is a pressing clinical need to consider second or third line 'off-label' medication option e.g. in treatment resistant mental health disorders such as depression, OCD or psychosis, then it is sensible to seek a second opinion to support the prescribing decision.

3. What to tell patients and families when prescribing 'off-label'

There is no legal requirement for a doctor to disclose the 'off-label' use of a drug to a patient. However, the GMC advice on prescribing is quite clear that sufficient information 'must' be given to enable informed consent to be given to any treatment including explaining the 'off-label' nature of prescribing to the patient (or carer as appropriate), and the reasons for doing so (General Medical Council 2013). Doctors must now ensure that patients (or their carers if the patient lacks legal capacity) are aware of any 'material risks' involved in a proposed treatment, and of reasonable alternatives, following the judgment in the case *Montgomery v Lanarkshire Health Board* (Montgomery (Appellant) v Lanarkshire Health Board (Respondent) (Scotland) 2015). This ruling moves away from the 'reasonable doctor' to the 'reasonable patient', and the Supreme Court's ruling outlined the new test: "The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it." Parents or young people reading a product insert or Summary of Product Characteristics (SPC) for an 'off-label' medication may be alarmed to read 'not recommended for people under age 18'. Therefore, we recommend that all drugs prescribed 'off-label' for children and adolescents are accompanied by an information sheet describing the use of the medication (including dosage and route of administration) for the prescribed indication (e.g. 'Use of clonidine in children to treat tics'). A helpful general leaflet written for parents and young people explaining 'off-label' and 'off-license' prescribing has been produced by Medicines for Children (Medicines for Children).

What do Guidelines say about 'off-label' prescribing?

Guidelines on 'off-label' prescribing have been produced by the Royal College of Psychiatrists (RCPsych) (Royal College of Psychiatrists 2007), the Royal College of Paediatrics and Child Health (RCPCH) (Royal College of Paediatrics and Child Health 2013), BNF for children (Paediatric Formulary Committee) and Medicines for Children (Medicines for Children). The RCPsych report (which covers all ages) notes that adverse reactions appear to be more common with unlicensed than with licensed products. Interestingly, the RCPCH guidelines state that where available 'an appropriate licensed preparation should be prescribed and supplied in preference to an unlicensed preparation'. However, the Medicines for Children guidance highlights situations when 'off-label'

prescribing may be safe and acceptable and the best clinical choice for a patient, for example being in a form that can be taken more easily by the child or because the unlicensed medicine is safer than a licensed one. We have already argued that rigid application of the RCPCH recommendations could lead to less effective and less safe medications compared to 'off-label' alternatives being prescribed to children and young people (e.g. Haloperidol for tics).

The BNF for Children (Paediatric Formulary Committee) states that as far as possible, medicines should be prescribed within the terms of the marketing authorisation but acknowledges that, many children require medicines not specifically licensed for paediatric use. Although medicines cannot be promoted outside the limits of the product licence, the Human Medicines Regulations (Medicines Regulatory Group 2012) do not prohibit the use of unlicensed medicines. The BNF for Children includes advice involving the use of unlicensed medicines or of licensed medicines for unlicensed uses ('off-label' use). Such advice reflects careful consideration of the options available to manage a given condition and the weight of evidence and experience of the unlicensed intervention. Where the advice falls outside a drug's marketing authorisation, BNF for Children shows the licensing status in the drug monograph and the indicated 'off-label' uses.

Recommendations

We propose the following principles when considering an 'off-label' trial of psychotropic medication for children and adolescents:

1. Be familiar with the evidence base for the psychotropic agent including its pharmacokinetic profile in children, the potential for adverse effects, any drug-drug interactions and differences in bioavailability/stability of the intended formulation.
2. Prescribing an 'off-label' medicine may have advantages over a licensed one. Hence, licensed drugs and formulations should not always be prescribed and supplied in preference to an 'off-label' drug or formulation. A prescribing decision (including a decision not to prescribe) should incorporate knowledge of the overall evidence-base and the needs of the individual child.

3. When the evidence-base for an 'off-label' medication is lacking or the benefit/risk profile appears potentially unfavourable, obtain a second opinion from another doctor (and perhaps another member of the multidisciplinary team) before prescribing.
4. Explain the potential benefits and side effects to the patient and their parents/carers and document this discussion.
5. Provide information leaflets for 'off-label' medications specifying use in children and adolescents including indications, dosage and route of administration.
6. 'Start low and go slow' and actively monitor response using standardised instruments and whether there are any adverse effects.

Summary and Next Steps

Healthcare professionals have a responsibility to prescribe the most effective and safe treatments for their patients. For children and adolescents, this may mean choosing an 'off-label' medication in preference to a licensed one, a non-pharmacological treatment or no treatment at all. The purpose of 'off-label' use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term 'off-label' does not imply an improper, illegal, contraindicated, or investigational use. 'Therapeutic decision making must always rely on the best available evidence and balance this against the risks and benefits for the individual patient' (Frattarelli et al. 2014).

There is an urgent need for better long-term pharmaco-epidemiological, safety and efficacy data on 'off-label' prescribing in children and adolescents. To date, there has been a far too narrow focus on short-term trials, with a lack of sufficient information on distal and lower frequency, but potentially serious adverse effects (Correll et al. 2013). In paediatric settings, insufficient attention has been devoted to the effects of commonly prescribed psychotropic medications on development, and too little is known about the safety and effectiveness of common 'off-label' prescribing.

The Paediatric Regulation and EMA guidance about the development of new medications for psychiatric disorders should improve the situation and ensure that all new medications for children are rigorously evaluated with adequate follow up to ascertain the safety profile in a paediatric setting. Programmes such as the FP7 funded ADDUCE study (ADDUCE) that is investigating the long term impact of methylphenidate on growth and development, cognitive and psychiatric effects and cardiovascular health and which is implementing the EMA guidance in the context of existing medications should be supported and built upon.

Further consideration should be given to allowing 'orphan drug' designation for certain 'off-label' psychotropic medications in order that they can benefit from the additional incentives offered for these medications. Epidemiological studies should focus on frequency of 'off-label' prescribing of psychotropic medications, the indications for their use and monitor secular trends. Large scale pharmacovigilance studies, perhaps utilising innovative designs (such as surveillance epidemiology (Smith et al. 2014)) and networks of investigators, should be conducted to assess the long term safety of existing drugs that are unlikely to be intensively investigated under the new regulations. These should be conducted in line with the standards set by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). In order to support research into medicines for children and provide a forum to bring together the regulators, researchers and industry, the EMA has created the European Networks for Paediatric Research and the EMA (ENPR-EMA). Ultimately research should include a focus on particularly vulnerable populations such as the very young, those with intellectual impairment and those with complex presentations and/or multiple comorbidities to benefit children and adolescents to receive the best and safest pharmacological care.

Conflicts of interest:

Dr Sharma, Prof Gringras, Mr Peter Pratt and Prof Hollis have no conflicts of interest

Dr. Arango has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Forum, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación,

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Prof Nutt has ownership or part ownership in Equasy Enterprises and Chaperon with interests in the area of psychopharmacology. He has acted as a consultant for Lundbeck, Nalpharm, Shire, MSD, Actelion. He has acted as an expert witness for Separator and received research grant income from Lundbeck. He has also accepted paid speaking engagements in industry supported symposia for Lundbeck, Otsuka, Lilly, BMS, Janssen, Glaxo Smith Kline, Pfizer, Astra Zeneca, D&A Pharma, Servier

Prof Young has been a consultant to or has received honoraria or grants from AstraZeneca, Lundbeck, Eli Lilly, Janssen, Servier, Sunovion, Cyberonics and Wyeth.

Box 1

The Paediatric Regulation (<http://bit.ly/1jLqHXM>)

The key measures included in the regulation are:

- ☐ The setting up of an expert committee within the EMA: the Paediatric Committee (PedCo)
- ☐ A requirement for companies to submit data on the use of a medicine in children in accordance with an agreed paediatric investigation plan (PIP) when applying for marketing authorisation for medicines or line-extensions for existing patent-protected medicines
- ☐ A system of waivers for medicines unlikely to benefit children
- ☐ A system of deferrals to ensure that medicines are tested in children only when it is safe to do so and to prevent a delay the authorisation of medicines for adults
- ☐ A reward for complying with the requirement in the form of a six-month extension to the Supplementary Protection Certificate
- ☐ For orphan medicines a reward for compliance in the form of an extra two years of market exclusivity added to the existing ten years awarded under the EU's Orphan Regulation
- ☐ A new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), to attract new paediatric indications for off-patent products
- ☐ Measures to maximize the impact of existing studies on medicines for children
- ☐ An EU inventory of the therapeutic needs of children to focus the research, development and authorisation of medicines
- ☐ An EU network of investigators and trial centres to carry out the required R&D (European Network of Paediatric Research at the European Medicines Agency, Enpr-EMA, <http://bit.ly/18hvTw8>)
- ☐ A system of free scientific advice for the industry, provided by the EMA
- ☐ A public database of paediatric studies
- ☐ A provision on EU funding for research to stimulate the development and authorisation of off-patent medicines for children.

The EMA has also included detailed guidance as to what evidence is required on paediatric populations before MA will be given to new medications for a range of psychiatric disorders. These regulations include a welcome focus on longer term safety and developmental issues. There is currently advice for:

- ☐ ADHD (<http://bit.ly/1O2XRPp>)
- ☐ Schizophrenia (<http://bit.ly/1GDBptm>)
- ☐ Depression (<http://bit.ly/1LRvvBN>)
- ☐ Autism (draft) (<http://bit.ly/1P12rMs>)

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